DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
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VIA FACSIMILE AND U.S. MAIL

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Re: Health Claim: Omega-3 Fatty Acids and Coronary Heart Disease
(Docket No. 91N-0103)

Dear Mr. Emord:

This letter is in reference to the court decision directing the Food and Drug Administration (FDA) to reconsider the health claim "Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease" in dietary supplement labeling (*Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999)). FDA has sent you replies on two of the other health claims that the court directed FDA to reconsider, namely, folic acid and neural tube defects and fiber and colorectal cancer. FDA will address, in a separate letter, the remaining health claim on antioxidants and cancer. We regret the delay in responding.

I. Procedure and Standard for Evaluating the Claim

In reconsidering this claim and the three other health claims that were the subject of *Pearson*, FDA has proceeded as described in the October 6, 2000, Federal Register notice entitled "Food Labeling; Health Claims and Label Statements for Dietary Supplements; Update to Strategy for Implementation of *Pearson* Court Decision" (hereinafter "the Pearson implementation notice")(65 Fed. Reg. 59,855 (2000)). As noted below in section IV, FDA first gathered new scientific evidence on the claims by contracting for a literature search and publishing two notices in the Federal Register soliciting comments and data. After reviewing the updated body of evidence on the claims, FDA applied the "significant scientific agreement" standard by which the health claim regulations require the agency to evaluate the scientific validity of claims. Under this standard, FDA may issue a regulation authorizing a health claim only "when it determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence." 21 C.F.R. § 101.14.

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For claims that did not meet the significant scientific agreement standard, FDA next considered whether to exercise enforcement discretion for qualified claims about the substance-disease relationship. Consistent with the *Pearson* opinion, the agency considered whether consumer health and safety would be threatened by the claim, and, if not, whether the evidence in support of the claim was outweighed by evidence against the claim, either quantitatively or qualitatively. See 164 F.3d at 650, 659 & n.10. If the evidence for the claim outweighed the evidence against the claim and there was no health or safety threat, the agency went on to consider whether a qualified claim could meet the general health claim requirements of 21 C.F.R. § 101.14, other than the requirement to meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. These requirements were not challenged in *Pearson* and therefore still apply.

In the Pearson implementation notice, FDA explained that it would consider exercising enforcement discretion for a dietary supplement health claim that did not meet the significant scientific agreement standard if the scientific evidence for the claim outweighed the scientific evidence against the claim, if the claim included appropriate qualifying language, and if the other criteria listed in the notice were met. In that event, the agency explained, FDA would send a letter to the petitioner outlining the agency's rationale for its determination that the evidence did not meet the significant scientific agreement standard and stating the conditions under which the agency would ordinarily expect to exercise enforcement discretion for the claim (65 Fed. Reg. at 59,856). The agency also stated that, conversely, if the scientific evidence for the claim did not outweigh the scientific evidence against the claim, or the substance posed a threat to health, or the other criteria for the exercise of enforcement discretion were not met, FDA would issue a letter denying the claim and explaining its reasons for doing so (65 Fed. Reg. at 59,856).

Although the deadlines for FDA action in 21 C.F.R. § 101.70(j) apply to health claims that are submitted by petition, they do not apply to the four claims that were the subject of *Pearson*. FDA is reconsidering those claims under a court order that sets no specific deadlines but clearly contemplates prompt action because of First Amendment concerns and the agency's obligation to comply with court orders as soon as possible. Accordingly, even though the deadlines in section 101.70(j) do not apply, FDA is using them as a guideline. Section 101.70(j)(2) requires the agency to issue a denial or a proposed regulation to authorize the health claim within 190 days of submission of the petition summarizing the scientific evidence relevant to the claim. FDA is issuing this decision letter on October 31, 2000, 211 days after the close of the second comment period for the submission of scientific evidence relevant to the claim.

II. Summary of Review

In the January 6, 1993 final rule concerning a health claim for the relationship between omega-3 fatty acids and coronary heart disease (CHD) for conventional food (hereinafter "the 1993 final rule"), FDA did not authorize a claim for omega-3 fatty acids and reduced risk of CHD (58 Fed. Reg. 2682 (1993)). FDA concluded in the 1993 final rule, based on: (1) The totality of the publicly available scientific evidence; and (2) the agency's review of comments

received in response to its November 27, 1991 proposed rule on omega-3 fatty acids and CHD (See 56 Fed. Reg. 60,663 (1991)) (hereinafter "the 1991 proposed rule"), there was not significant scientific agreement among experts that such evidence supported a health claim for omega-3 fatty acids and CHD (58 Fed. Reg. at 2682). As explained in more detail in section IV.A. below, FDA also denied a health claim for omega-3 fatty acids and reduced risk of CHD for dietary supplements.[1]

In its 1991-1993 review of the scientific evidence for omega-3 fatty acids and reduced risk of CHD, FDA limited its review to two omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). FDA did not include the omega fatty acid, linolenic acid, in its review. Unlike EPA and DHA which are derived from fish oils and from fish, linolenic acid is derived primarily from plant sources. FDA limited its review to EPA and DHA because the hypothesis for a relationship between omega-3 fatty acids and CHD derived from correlations between low rates of CHD and high consumption of fish oils. In addition, most of the information about the effects of omega-3 fatty acids on CHD was derived from studies of fish oils or fish consumption. Furthermore, only a limited amount of linolenic acid is converted in the body to EPA and DHA. Therefore, FDA concluded that the potential nutrient/disease relationship was appropriately limited to EPA and DHA and their effect on CHD risk. See 58 Fed. Reg. at 2683. FDA's conclusion has not changed. Consequently, the agency is similarly limiting its current review to the relationship between EPA and DHA and reduced risk of CHD. Thus, when the term "omega-3 fatty acids" is used in this letter, FDA means only EPA and DHA omega-3 fatty acids, unless otherwise noted.

In the 1993 final rule, FDA noted that, although there was evidence for effects of omega-3 fatty acids on clinical measures that may be related to the risk of CHD, such as reduction in fasting and postprandial triglycerides, reductions in platelet aggregation and adhesion, and changes in the composition of lipoproteins, qualified experts did not generally agree at the time that these endpoints were closely related to the risk of CHD (58 Fed. Reg. at 2706). Furthermore, the available data from diet studies that reported a relationship between fish consumption and CHD could not demonstrate that the observed effects were due to the omega-3 fatty acids in the fish. Thus, FDA concluded that there was not significant scientific agreement among qualified experts that the totality of the publicly available scientific evidence supported a health claim for omega-3 fatty acids and reduced risk of CHD (*id.* at 2682).

In response to *Pearson*, FDA has considered whether the use of EPA and DHA omega-3 fatty acids are safe and lawful, as required under 21 C.F.R. § 101.14(b)(3)(ii) for dietary supplements. FDA has also reconsidered the scientific evidence on the relationship between omega-3 fatty acids and the risk of CHD. The agency concentrated on the human studies that have become available since the original omega-3 fatty acids-CHD rulemaking that concluded

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[1] A proposed rule for the dietary supplement health claim on omega-3 fatty acids and reduced risk of CHD (58 Fed. Reg. 53,296 (1993)) became a final regulation by operation of law (59 Fed. Reg. 436 (1994)). FDA relied on the scientific review conducted as part of the omega-3 fatty acid-CHD health claim rulemaking for conventional foods, that concluded in January 1993, for the 1993 dietary supplement proposed rulemaking for the same claim.

in 1993. Both the agency's original 1991-1993 scientific evaluation and the evaluation of the evidence that has become available since that time were conducted consistent with the principles and procedures articulated in FDA's *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements* (December 1999).

Based upon its review of the safety of EPA and DHA omega-3 fatty acids and its review of the scientific evidence, FDA finds that: (1) the use of EPA and DHA omega-3 fatty acids as dietary supplements is safe and lawful under 21 C.F.R. § 101.14, provided that daily intakes of EPA and DHA omega-3 fatty acids do not exceed three grams per person per day (3 g/p/d) from conventional food and dietary supplement sources; (2) although the totality of the publicly available scientific evidence demonstrates a lack of significant scientific agreement as to the validity of a relationship between omega-3 fatty acids and reduced risk of CHD in the general population, the scientific evidence in support of a qualified claim[2] outweighs the scientific evidence against the claim; and (3) it may appropriately exercise enforcement discretion with respect to the use of the qualified claim about the strength of the scientific evidence in the general population, provided that the general conditions stated in the Pearson implementation notice and the specific conditions set forth in this letter are met.

III. Safety Review

A. Background

Under 21 C.F.R. § 101.14(b)(3)(ii), which was not challenged in *Pearson* and which still applies to FDA's review of a proposed dietary supplement health claim, the use of EPA and DHA omega-3 fatty acids, at levels necessary to justify a claim, must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful.[3]

The safety provisions in question require, for example, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling or under ordinary conditions of use (21 U.S.C. 342(f)(1)). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render

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[2] The qualified claim is discussed further in section VI and states that: "The scientific evidence about whether omega-3 fatty acids may reduce the risk of coronary heart disease (CHD) is suggestive, but not conclusive. Studies in the general population have looked at diets containing fish and it is not known whether diets or omega-3 fatty acids in fish may have a possible effect on a reduced risk of CHD. It is not known what effect omega-3 fatty acids may or may not have on risk of CHD in the general population."

[3] In this case, there is no proponent of the claim submitting safety data in a health claim petition. FDA is responding to instructions from the U.S. Court of Appeals for the D.C. Circuit to reconsider the health claim and is not responding to a petition. Further, as discussed later in this letter, based on the agency's scientific review, the relationship between EPA and DHA omega-3 fatty acids and CHD for the general population is merely suggestive, and therefore, to suggest that sufficient evidence is available to support a specific daily dietary intake that would be necessary to achieve a claimed effect would be false and misleading under sections 201(n) and 403(a) of the Federal Food, Drug, and Cosmetic Act (the act). Consequently, FDA evaluated whether, and in what amount, EPA and DHA omega-3 fatty acids, when used in a dietary supplement, would be safe in the context of the total daily diet.

the supplement injurious to health under the conditions of use recommended or suggested in the labeling (21 U.S.C. 342(f)(1)(D)). Ensuring the safety of a dietary supplement that may bear a qualified claim is also consistent with the *Pearson* decision, in which the court stated that the agency could be justified in banning certain health claims outright if, for example, consumer health and safety would be threatened (see *Pearson*, 164 F.3d 650 at 657-60).

In its safety review in this matter, FDA considered its earlier safety reviews, including the 1991 proposed rule concerning omega-3 fatty acids and CHD and the 1993 final rule. In addition, FDA reviewed its June 5, 1997 final rule in which the agency affirmed that menhaden oil, a fish oil in which EPA and DHA are the major sources of omega-3 fatty acids, is generally recognized as safe (GRAS), within specific limitations of use (62 Fed. Reg. 30,751 (1997)).

In the 1991 proposed and 1993 final rules, FDA discussed safety concerns relating to omega-3 fatty acid intake. These safety concerns included: (1) increased bleeding times, (2) the possibility of hemorrhagic stroke, (3) oxidation of omega-3 fatty acids forming biologically active oxidation products, (4) increased levels of low density lipoproteins (LDL) cholesterol or apoproteins associated with LDL cholesterol among diabetics and hyperlipidemics, and (5) reduced glycemic control among diabetics. See 56 Fed. Reg. at 60,671; 58 Fed. Reg. at 2699, 2704-2705. FDA concluded in its 1993 final rule that there were significant unresolved safety concerns relating to intake of omega-3 fatty acids (see 58 Fed. Reg. at 2706).

In its 1997 final rule affirming that menhaden oil, with specific limitations, is GRAS as a direct human food ingredient (62 Fed. Reg. 30,751), FDA examined the scientific literature for evidence that consumption of fish oils may contribute to increased bleeding time, reduced glycemic control in non-insulin dependent diabetics, and increased LDL cholesterol (*id.* at 30,752-30,754). FDA concluded that the use of menhaden oil as a direct food ingredient is safe, provided that daily intakes of EPA and DHA, which are the primary omega-3 fatty acids found in fish, do not exceed 3 g/p/d. The agency affirmed menhaden oil as GRAS under 21 C.F.R. § 184.1(b)(2). The specific limitations of use under that regulation established maximum use levels for specific food categories in which menhaden oil may be used. FDA established maximum use levels and food use categories to ensure that the mean intake of menhaden oil would be less than 3 grams of EPA and DHA per day, thus ensuring that dietary intake would not exceed 3 g/p/d.

In the GRAS rule for menhaden oil, increased bleeding times was the adverse event associated with the lowest intake level (62 Fed. Reg. at 30,753). Thus, in this matter, the safety review under section 101.14 for EPA and DHA omega-3 fatty acids as a dietary supplement focused on increased bleeding times and associated risks such as hemorrhagic stroke. FDA also evaluated the scientific literature for safety concerns in addition to those safety concerns identified in the GRAS affirmation rule for menhaden oil and in the 1991 proposed rule and the 1993 final rule for omega-3 fatty acids.

In its 1993 final rule, FDA reported that increased omega-3 fatty acid intakes have been associated with increased bleeding and prothrombin times, which are related to the possibility of increased occurrence of stroke (58 Fed. Reg. at 2695). The agency noted that the studies

that reported a correlation between high intakes of omega-3 fatty acids and low rate of CHD mortality also noted an increased rate of stroke, particularly hemorrhagic stroke. Similar types of concerns have also been raised by the data from studies on aspirin (*id.* at 2699).

Significant concerns relating aspirin to bleeding times were raised in the preamble to the final rule for the professional labeling of aspirin (63 Fed. Reg. 56,802 at 56,804 (1998)). In that preamble, FDA discussed bleeding problems and risk of hemorrhagic stroke. The agency noted that use of aspirin by participants in the aspirin component from the U.S. Physicians' Health Study (Steering Committee of the Physicians' Health Study Research Group, 1989) was accompanied by an increase in strokes, especially severe, fatal, hemorrhagic stroke; by a greater incidence of sudden death and "other" cardiovascular deaths; by more frequent cerebral hemorrhage as a cause of stroke; and by increased incidence of other adverse effects, including bleeding problems and the need for transfusion (63 Fed. Reg. at 56,804). FDA noted that one aspirin subject died from gastro-intestinal bleeding (*id.*). Because of associated risks, the agency did not support the labeling of aspirin products for prophylactic use to prevent first myocardial infarction (MI) in the general population even though the studies suggested such use as a preventive measure for some people.

Because omega-3 fatty acids, like aspirin, extend bleeding times (62 FR at 30,753), it is important to consider the intake of omega-3 fatty acids that, based on currently available evidence, is <u>not</u> likely to pose a health risk to the general population and that minimizes the potentially serious side effects, such as unwarranted bleeding and the serious consequences that may result. In the GRAS affirmation review for menhaden oil, FDA reviewed the available evidence that noted changes in bleeding times associated with the use of EPA and DHA and concluded that there is no significant risk for increased bleeding time beyond the normal range, provided consumption of fish oils is limited to 3 grams or less per person per day of EPA and DHA (62 Fed. Reg. at 30,753). Therefore, provided that daily intakes of EPA and DHA omega-3 fatty acids from conventional foods and dietary supplements do not exceed 3 g/p/d, FDA believes that the use of EPA and DHA omega-3 fatty acids as a dietary supplement will not pose a health risk to the general population.

Because EPA and DHA appear to inhibit a number of immune cell functions when evaluated *in vitro* and in animal and human models, concerns have recently been raised that increased intakes of omega-3 fatty acids could lead to suppression of immune and inflammation responses, and consequently, to decreased resistance to infections and increased susceptibility to opportunistic bacteria (Kelley and Rudolph, 2000; Calder, 1998; deDeckere, et al., 1998; Meydani and Dinarello, 1993). These studies, which have been limited to *in vitro* studies, animal studies, and small studies in humans require additional information to determine whether there is an effect of omega-3 fatty acids on immune function that would raise safety concerns, especially in populations with diminished immune function, e.g., the elderly and people with Human Immunodeficiency Virus (HIV) at intakes less than 3 grams/day.

B. Upper Safe Intake Limits

In its GRAS affirmation review for menhaden oil, FDA concluded that the use of menhaden oil as a direct food ingredient is safe, provided that daily intakes of EPA and DHA from

menhaden oil do not exceed 3 g/p/d. The agency established specific limitations, i.e., maximum use levels for 17 food categories in which menhaden oil may be used (62 Fed. Reg. at 30,757). These levels were established to ensure that the mean intake would be less than 3 grams of EPA and DHA per person per day. It is important to note that this exposure did not include intakes from dietary supplements or from conventional food ingredient and food sources of EPA and DHA other than menhaden oil.

Based on the data and information that FDA considered, which includes data and information that FDA relied upon in reaching its conclusions about the safety of EPA and DHA omega-3 fatty acids in its GRAS affirmation of menhaden oil, the data and information in the 1991 proposed and 1993 final rules, and its current scientific literature review for other possible safety concerns, FDA concludes that the use of EPA and DHA omega-3 fatty acids as dietary supplements is safe and lawful under 21 C.F.R. § 101.14, provided that daily intakes of EPA and DHA omega-3 fatty acids do not exceed 3 g/p/d from conventional food and dietary supplement sources. In section VI.B.2, FDA sets forth conditions, under which it plans to exercise its enforcement discretion for EPA and DHA dietary supplements bearing the qualified claim, to ensure, among other things, that such use will be safe.

IV. Review of the Scientific Evidence

A. 1991-1993 Scientific Review

Congress enacted the health claim provisions of the Nutrition Labeling and Education Act of 1990 (NLEA) to help consumers maintain good health through appropriate dietary patterns and to protect consumers from unfounded health claims. The NLEA specifically required the agency to determine whether claims respecting 10 nutrient/disease relationships met the statutory requirements for health claims (Pub. L. 101-535, § 3(b)(1)(A), 104 Stat. 2353, 2361). The relationship between omega-3 fatty acids and heart disease was one of these 10 claims that Congress required the agency to evaluate.

FDA began its review of these 10 claims by publishing a notice in the March 28, 1991, Federal Register requesting scientific data and information relevant to the claims. See 56 Fed. Reg. 12,932. The agency also contracted with the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) for an independent scientific review of recent evidence on omega-3 fatty acids and CHD. In November 1991, FDA published a proposed rule setting forth its review of available scientific evidence and tentative conclusions with respect to authorization of a health claim for the relationship between omega-3 fatty acids and CHD (56 Fed. Reg. 60,663 (1991)). In the 1991 proposed rule, the agency did not propose to authorize such a health claim for either dietary supplements or conventional foods, tentatively concluding that the evidence did not provide a basis upon which to authorize a health claim relating to an association between omega-3 fatty acids and reduced risk of CHD (*id.* at 60,663). FDA noted that the epidemiological research on the topic applied only to the consumption of fish, which contain omega-3 fatty acids, and that it was not possible to ascribe any effects specifically to the omega-3 fatty acids (*id.*). The agency also stated that the data from clinical studies revealed that omega-3 fatty acids had no effect on serum cholesterol, LDL cholesterol, or HDL cholesterol, the blood lipid variables

most closely associated with risk of CHD. FDA also noted that there were unresolved safety issues relating to intake of omega-3 fatty acids, specifically, the potential for omega-3 fatty acids to increase LDL cholesterol of hyperlipidemics and to worsen control of blood glucose in diabetics (*id.*). The agency did not propose to authorize a health claim relating to the association between omega-3 fatty acids and CHD based on its review of the scientific evidence.

While the proposed rule was pending, Congress passed the Dietary Supplement Act of 1992 (the DSA) (Pub. L. No. 102-571, 106 Stat. 4500). The DSA imposed a moratorium on FDA's implementation of the NLEA with respect to dietary supplements until December 15, 1993. The DSA also directed FDA to repropose implementing regulations for dietary supplements by June 15, 1993, and provided that the proposed regulations would become final by operation of law if final rules were not issued by December 31, 1993.

In the 1993 final rule, FDA concluded that there was not significant scientific agreement among experts that the evidence supported a health claim for omega-3 fatty acids and CHD (58 Fed. Reg. at 2682). In particular, FDA noted that only a few studies found a relationship between fish intake and CHD, while others found none; thus, there was no consistency of findings (*id.* at 2706). In addition, none of the studies that reported a relationship between fish intake and CHD distinguished fish consumption from other factors associated with fish consumption (*id.*). Therefore, it was not possible to determine whether the effects observed were due to omega-3 fatty acid intake or to some other factor associated with fish consumption.

The agency also reviewed the study data relating omega-3 fatty acid intake to total cholesterol and to LDL cholesterol (*id.* at 2706). FDA noted that these studies did not find decreased total or LDL cholesterol in normal, healthy persons, or among persons at risk for CHD from consumption of omega-3 fatty acids (*id.*).

Further, FDA concluded that although there was evidence for effects of omega-3 fatty acids on factors that may be related to risk of CHD, such as reduction in fasting and postprandial triglycerides, reductions in platelet aggregation and adhesion, and changes in the composition of lipoproteins, qualified experts did not generally agree at the time that these endpoints were closely related to the risk of CHD (*id.* at 2706-2707). Overall, FDA concluded that the available evidence was not sufficient to demonstrate a relationship between omega-3 fatty acids and reduced risk of CHD (*id.* at 2706). Therefore, FDA did not authorize a health claim for a relationship between intake of omega-3 fatty acids and the risk of CHD.

Because of the DSA's moratorium on implementation of the NLEA with respect to dietary supplements, the 1993 final rule applied only to health claims for conventional foods, not dietary supplements. In response to the DSA's directive to issue proposed regulations specific to dietary supplements, FDA proposed, in October 1993, not to authorize a health claim for omega-3 fatty acids and CHD in the labeling of dietary supplements (58 Fed. Reg. 53,296(1993)). The October 1993 proposal relied on the scientific review conducted as part of the omega-3 fatty acid-CHD health claim rulemaking that concluded in January 1993.

FDA did not issue a final rule by December 31, 1993, and therefore, the October 1993 proposal became final on January 4, 1994 (59 Fed. Reg. 436 (1994)).

B. Current Scientific Review

FDA's first step in reconsidering the health claim for omega-3 fatty acids and reduced risk of CHD in response to *Pearson* was to gather the relevant scientific evidence that had become available since the previous rulemaking on this topic. To update its earlier review, the agency reviewed comments[4] and data submitted in response to two Federal Register notices requesting scientific data and information, as well as data identified in a literature search. See 64 Fed. Reg. 48,841 (1999) and 65 Fed. Reg. 4252 (2000). The literature search covered publications that were issued after 1991.

During its 1991-93 review, FDA considered preclinical studies (studies not performed in humans) because they are useful for developing hypotheses or investigating mechanisms of putative relationships between food substances and physiological changes associated with disease risk. However, the usefulness of data from preclinical studies is limited in that such studies cannot fully simulate human disease and physiology. Additionally, preclinical studies cannot accurately estimate appropriate intake levels or the size of effects in humans. Since FDA's 1991-93 review, a number of well-designed new human studies have become available. In the current review, therefore, FDA focused on human studies that quantitatively measured or estimated the omega-3 fatty acid intakes in relation to a direct measure of CHD risk or a surrogate marker for CHD risk (see Tables 1-3).

1. Intervention Trials

In an intervention study, the investigator controls whether the subjects receive an exposure (the intervention), whereas in an observational study, the investigator does not have control over the exposure. Therefore, intervention studies generally provide the strongest evidence for an effect. Unlike observational studies, which provide evidence of an association, but not necessarily of a cause and effect relationship, between the substance and disease of interest, intervention studies can provide evidence of causal relationships or the lack thereof. Randomized controlled clinical trials are considered the most persuasive studies. When the results of such studies are available, they will be given the most weight in the evaluation of the totality of the evidence. See *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements*, at 5.

A number of randomized, controlled, clinical intervention trials of omega-3 fatty acids and reduced risk of CHD have been published since 1992. These studies directly addressed the intake of EPA and DHA in diseased populations in relation to a CHD endpoint (e.g., cardiovascular death, non-fatal MI) (Table 1). These studies were the most useful because they provided specificity regarding measurement of the substance, measurement of the

[4] FDA received three comments after the close of the comment period. The agency was not obligated to and did not consider the late comments. All other comments were considered.

disease or health-related condition, and evidence for a relationship (in a diseased population only) between the substance and the disease or health-related condition.

The intervention trials with CHD as the endpoint ranged in length from 1 year to 3.5 years and in size from 223 people in one study location to 11,324 people in 172 separate centers (Table 1). These studies were conducted in diseased populations, i.e., subjects with diagnosed CHD or recent MIs (GISSI Prevensione Investigators, 1999; von Schacky, et al., 1999; Singh, et al., 1997; Burr, et al., 1994). They all reported significant reductions in CHD risk with increased consumption of omega-3 fatty acids, predominantly EPA and DHA, although one study also included mustard oil, which contains alpha-linolenic acid (ALA), an omega-3 fatty acid derived primarily from plant sources (Singh, et al., 1997). In particular, the largest study, the GISSI trial (GISSI Prevensione Investigators, 1999), conducted in patients who had survived a recent MI, reported a 15 percent decrease in relative risk of CHD (defined as death, non-fatal MI, and non-fatal stroke) in the intervention group that consumed 850-882 mg/d of ethyl esters of EPA and DHA (in a 1:2 ratio).

The agency also considered the scientific evidence from a number of intervention studies relating intake of omega-3 fatty acids to levels of LDL cholesterol, a validated surrogate marker for CHD risk (Table 2). Most of the intervention studies that measured blood lipids, both in general and diseased populations, reported no significant differences in LDL cholesterol (Sorensen, et al., 1998; Vognild, et al., 1998; Grimsgaard, et al., 1997; Hwang, et al., 1997; Marckmann, et al., 1997; Agren, et al., 1996; Hamazaki, et al., 1996; Layne, et al., 1996; Lervang, et al., 1993; Deslypere, 1992; Schmidt, et al., 1992; GISSI Prevensione Investigators, 1999; Cairns, et al. 1996; Eritsland, et al., 1996; Eritsland, et al., 1995; Sacks, et al., 1995; Eritsland, et al., 1994; Leaf, et al., 1994). Several of these intervention studies reported increased levels of LDL cholesterol (Adler, et al., 1997; Mori, et al., 1994; Hansen, et al., 1993; Sirtori, et al., 1998), and Morcos (Morcos, 1997) reported decreased levels of LDL cholesterol in response to intake of omega-3 fatty acids in dietary supplements. Thus, most of the intervention studies that measured LDL cholesterol did not support a relationship between omega-3 fatty acids and reduced risk of CHD either in diseased or general populations.

In particular, the GISSI trial (GISSI Prevensione Investigators, 1999), the clinical trial with the longest duration (3.5 years), the largest sample size (n = 11,324), and that measured both LDL cholesterol and CHD in a diseased population, reported that there were no statistically significant changes in LDL cholesterol, while also reporting a 15-percent-decrease in relative risk of CHD in the diseased population intervention group that consumed omega-3 fatty acids (Tables 1 and 2). Thus, in most of the intervention studies, including the GISSI trial with the largest sample size and the longest duration, omega-3 fatty acids showed a reduction of risk for CHD in a diseased population, but the effect is apparently not working through a mechanism of LDL cholesterol reduction.

The agency did not consider other markers for CHD risk either because they are weaker biomarkers than LDL cholesterol (e.g., total cholesterol) (National Cholesterol Education Program, 1993; Trans Fatty Acids proposed rule, November 17, 1999, 64 Fed. Reg. 62746, at 62,768-62,770) or because they are not generally agreed to be closely related to the risk of

CHD (e.g., reductions in platelet aggregation and adhesion, and changes in the composition of lipoproteins)(58 Fed. Reg. at 2707).

Thus, the scientific evidence from intervention studies with EPA and DHA omega-3 fatty acids as the test substance, did not show a relationship between omega-3 fatty acids and reduced risk of CHD in the general population. Because there are no comparable studies with CHD as their endpoint in the general population, it is not known whether the effect in the general population would be the same as the effect found in a diseased population. Further, omega-3 fatty acids generally have no effect on LDL cholesterol, a validated surrogate marker for CHD, and, therefore, are not useful in establishing, through the mechanism of lowering LDL cholesterol, a direct benefit of omega-3 fatty acids on reduced risk of CHD for the general population. Since definitive evidence on a relationship between omega-3 fatty acids and reduced risk of CHD in the general population was not demonstrated by interventional data, the agency considered whether available observational data provided support for a relationship between omega-3 fatty acids and reduced risk of CHD.

2. Observational Studies

Observational studies (sometimes called "epidemiological" studies) include several types: population or correlational, retrospective case control, and prospective cohort. These types of studies can provide information on the association between omega-3 fatty acids and CHD; however, these studies often do not provide a sufficient basis for determining whether a substance-disease association reflects a causal, rather than a coincidental, relationship. Population or correlational studies use grouped data to examine the relationship between dietary exposure and health outcome among populations. Such studies do not examine relationships for individuals and have traditionally been regarded as useful for generating, rather than testing, hypotheses regarding diet-disease relationships. Therefore, FDA did not give population studies as much weight in the current evaluation. In case-control studies, subjects with existing diagnosed disease (the cases) are enrolled in a study. These subjects are matched by identifiable characteristics (e.g., age, race, gender) to disease-free subjects (the controls). The diets of the two groups are then compared to discern dietary habits associated with risk for the disease. In prospective, or cohort, studies, disease-free subjects are recruited within a specified group of people, such as female nurses (the cohort), and the dietary habits of the subjects are determined. The study tracks the subjects over an extended period of time to see whether they develop the disease being investigated. At the end of the follow-up period, the dietary patterns of subjects who developed the disease during the follow-up period are compared to those of the subjects who did not develop the disease to discern dietary patterns that are associated with risk of the disease. Prospective studies are generally considered to be the most persuasive type of observational study. Therefore, FDA weighted these more heavily than other types of observational studies.

An inherent limitation of all these types of dietary observational studies is the extent to which omega-3 fatty acid intake can be assessed. There is considerable uncertainty in the quantitative measurement of habitual food intake over long periods of time. Some studies typically used a retrospective food frequency questionnaire in which the study subjects are asked to recall their typical diets (in terms of foods eaten, frequency of eating, and serving

sizes) over several previous years (Ascherio, et al., 1995; Daviglus, et al., 1997; Pietinen, et al., 1997; Albert, et al., 1998; Kromhout, et al., 1996; Rodriguez, et al., 1996; Kromhout, et al., 1995; Morris, et al., 1995; Simon, et al., 1995; Siscovick, et al., 1995). Such techniques are subject to recall bias, particularly for dietary factors thought possibly related to disease. Other sources of error occur in the translation of food intake data into omega-3 fatty acid intake data by calculation from food composition tables. The natural variability of foods and the lack of validated analytical methods for the whole range of types of foods make it difficult to accurately calculate omega-3 fatty acid intake from food intake data. Moreover, diets containing omega-3 fatty acid sources differ in other components (e.g., saturated fats) from diets that do not contain such sources. This makes it difficult to establish whether omega-3 fatty acids or some other component of the diet is responsible for any observed benefit. In short, there are significant limitations to assessing omega-3 fatty acid intake data from observational studies and relating intake to the disease. Since the primary variable assessed in these studies is food consumption, and there are multiple sources of error involved in estimating omega-3 fatty acids intake from such data, the usefulness of these types of studies to differentiate effects of the omega-3 fatty acids in the food from effects of other components of the food is more limited than are intervention studies where such factors can be better controlled.

As a consequence of their inherent shortcomings, observational studies are of limited use in resolving the key issue from the 1993 evaluation. In other words, one cannot determine from such studies whether omega-3 fatty acids are in fact the agents that provided any benefit in reducing the risk of CHD that might have been observed. Nonetheless, FDA considered recent observational studies from among the available evidence to see if such studies provided a sufficient basis for the agency to be able to generalize to the general population the effects seen in a diseased population in the well done intervention trials.

Some observational studies estimated omega-3 fatty acid intake directly from measurements of omega-3 fatty acids in body tissues or fluids (e.g., subcutaneous adipose tissue, blood samples, red blood cell membrane) (Guallar, et al., 1999; Guallar, et al., 1995; Simon, et al., 1995; Siscovick, et al., 1995; Yamori, et al., 1994). However, measures of omega-3 fatty acids in body tissues or fluids can be affected by how food components are metabolized, stored, and used in the body. Also, these measures could be a marker for dietary factors other than omega-3 fatty acids. Because of the inherent limitations of observational studies in estimating omega-3 fatty acid intakes from food frequency questionnaires and body tissues or fluids, FDA placed less weight on these studies as evidence that dietary supplements of omega-3 fatty acids may reduce risk of heart disease.

The recently available observational trials with CHD as the endpoint included prospective cohort and case-control studies and ranged in length from a single snapshot in time to 30 years in length and in size from 188 to 44,895 people in a single location or in 19 centers in 14 countries (Table 3). FDA focused primarily on the prospective studies and the nested case control components of prospective studies because prospective studies are generally considered the most persuasive type of observational study (Ascherio, et al., 1995; Daviglus, et al., 1997; Pietinen, et al., 1997; Albert, et al., 1998; Kromhout, et al., 1996; Rodriguez, et al., 1996; Guallar, et al., 1995; Kromhout, et al., 1995; Morris, et al., 1995; Simon, et al.,

1995). These studies were in populations that were disease-free at baseline. Of these, all but the Ascherio (Ascherio, et al., 1995), the Pietinen (Pietinen et al., 1997), the Guallar (Guallar, et al., 1995), and the Morris (Morris, et al., 1995) studies showed a decreased risk of CHD with increasing consumption of fish.

The longest study, the 30-year cohort study of Daviglus used detailed dietary histories to stratify, into four groups, the fish consumption of 1822 men, who were free of cardiovascular disease at baseline (Daviglus, et al., 1997). The study reported that fish consumption was inversely associated with mortality from CHD (defined as death from MI, sudden or non-sudden, or death from other coronary causes). This long, extensive study in a general population suggests a dose-response relationship between fish consumption and risk of CHD, which supports the hypothesis that omega-3 fatty acids in fish may reduce the risk of CHD in the general, fish-consuming population.

By contrast, the largest study, the 10-year Ascherio cohort study related total dietary omega-3 fatty acid intake, estimated from food frequency questionnaires, to CHD risk in 44,895 males who were disease-free at baseline (Ascherio, et al., 1995). This large, long-term study in a general population reported no association between intake of omega-3 fatty acids from fish or from fish oil supplements and reduction of risk of coronary disease or CHD endpoint.

Of three published reports from the Physicians' Health Study (Albert, et al., 1998; Guallar, et al., 1995; Morris, et al., 1995), two of these reports, based on 4- to 5-years of follow-up data, showed no relationship between fish intake or blood levels of omega-3 fatty acids and CHD risk (Guallar, et al., 1995; Morris, et al., 1995). Conversely, one of these three reports, that was a 12-year follow-up of the Physician's Health Study, did show a relationship between fish intake and decrease in sudden cardiac disease (Albert, et al., 1998), suggesting that longer term follow-up enhances the likelihood of seeing an effect.

One of the studies suggested increased risk of CHD with increasing intake of omega-3 fatty acids (Pietinen, et al., 1997); however, this study was conducted in a population of Finnish smokers, which raises questions about its applicability to the general population.

The other observational study data are equivocal with two showing benefit for omega-3 fatty acids on CHD risk (Siscovick, et al., 1995; Yamori, et al., 1994) and one showing no effect (Guallar, et al., 1999).

In sum, the two prospective studies that had the most statistical power (Daviglus, et al., 1997; Ascherio, et al., 1995) showed divergent results about the relationship between omega-3 fatty acids and reduced risk of CHD. The three reports on the Physicians' Health Study (Albert, et al., 1998; Guallar, et al., 1995; Morris, et al., 1995) showed an effect after 12 years that was not seen at 4 and 5 years. The one study that suggested an adverse effect (Pietinen, et al., 1997) was in a select population. The four remaining prospective studies (Kromhout, et al., 1996; Rodriguez, et al., 1996; Kromhout, et al., 1995; Simon, et al., 1995) showed decreased risk of CHD with increasing intakes of omega-3 fatty acids. The other observational studies (Siscovick, et al., 1995; Yamori, et al., 1994; Guallar, et al., 1999) were generally equivocal.

Thus, FDA concludes that the observational study data are mixed for a relationship between fish intake and reduced risk of CHD. Several studies show no relationship or suggest an adverse effect (Ascherio, et al., 1995; Guallar, et al., 1999; Pietinen, et al., 1997; Guallar, et al., 1995; Morris, et al., 1995); and others suggest a relationship between fish intake and reduced risk of CHD (Daviglus, et al., 1997; Albert, et al., 1998; Kromhout, et al., 1996; Rodriguez, et al., 1996; Kromhout, et al., 1995; Simon, et al., 1995; Siscovick, et al., 1995; Yamori, et al., 1994). Observational study data reflect the total diet of individuals, and as such, show the effect of many factors in addition to omega-3 fatty acids.

Further, the current *Dietary Guidelines for Americans*, 2000, federal government guidance on healthy eating practices, specifically mentions omega-3 fatty acids and states: "Some fish, such as salmon, tuna, and mackerel, contain omega-3 fatty acids that are being studied to determine if they offer protection against heart disease." It is apparent from this statement, as well as from the observational studies discussed earlier, that additional study is needed to determine if the omega-3 fatty acids per se in the fish are specifically and causally related to reduced risk of CHD. The recent observational data are equivocal for a relationship between omega-3 fatty acids per se and reduced risk of CHD, and do not resolve uncertainties as to the effectiveness of omega-3 fatty acids on CHD risk in the general population. As such, these results do not alter the agency's 1993 determination that there is no consistency of findings among these observational studies and that the studies do not distinguish fish consumption from other factors associated with fish consumption.

V. The Agency's Consideration of Significant Scientific Agreement (SSA)

In its 1993 final rule on omega-3 fatty acids and reduced risk of CHD, FDA noted that none of the studies (surveys, cross-sectional studies, nonintervention prospective studies and intervention studies) provided evidence to attribute benefit, when observed, to omega-3 fatty acid intake rather than to some other factor associated with fish consumption (58 Fed. Reg. at 2706). Thus, the studies lacked specificity for the substance that was the subject of the claim in relationship to CHD. In evaluating whether there is significant scientific agreement for a relationship between omega-3 fatty acids and reduced risk of CHD, FDA focused, therefore, on studies that could address this lack of specificity that was reported in the 1993 final rule. FDA finds that the more recent data do not alter the previous 1993 determination that the scientific evidence is not sufficiently conclusive or specific for omega-3 fatty acids to justify the use of a health claim relating the intake of omega-3 fatty acids and reduced risk of CHD in the general population.

The newer intervention trials for omega-3 fatty acids and reduced risk of CHD that had CHD as the endpoint (GISSI Prevensione Investigators, 1999; von Schacky, et al., 1999; Singh, et al., 1997; Burr, et al., 1994) show that, in diseased populations (i.e., subjects with diagnosed CHD or recent MI), increased intakes of omega-3 fatty acids are related to reduced risk of CHD. However, there are no studies directly relating omega-3 fatty acids and CHD in the general population that could isolate the effect of omega-3 fatty acids and that had CHD as the endpoint; therefore, there is uncertainty regarding the effect of omega-3 fatty acid intake in the general population. There is some information from observational trials relating fish consumption and reduced risk of CHD (Daviglus, et al., 1997; Pietinen, et al., 1997; Albert, et

al., 1998; Kromhout, et al., 1996; Rodriguez, et al., 1996; Kromhout, et al., 1995; Simon, et al., 1995; Siscovick, et al., 1995; Yamori, et al., 1994). However, it is not possible to determine whether the effects observed were due to omega-3 fatty acid intake or to some other factor associated with fish consumption; therefore, there is uncertainty regarding specificity for the substance, omega-3 fatty acids. Furthermore, the observational study results were mixed, with some studies showing no relationship and others suggesting benefit for omega-3 fatty acids on CHD risk; thus, the observational studies are equivocal for an effect of omega-3 fatty acids on reduced risk of CHD.

There are many new intervention studies that measured omega-3 fatty acid intake in conjunction with LDL cholesterol, a validated surrogate marker for CHD (Sorensen, et al., 1998; Vognild, et al., 1998; Adler, et al., 1997; Grimsgaard, et al., 1997; Hwang, et al., 1997; Marckmann, et al., 1997; Morcos, 1997; Agren, et al., 1996; Hamazaki, et al., 1996; Layne, et al., 1996; Mori, et al., 1994; Hansen, et al., 1993; Lervang, et al., 1993; Deslypere, 1992; Schmidt, et al., 1992; GISSI Prevensione Investigators, 1999; Cairns, et al., 1996; Eritsland, et al., 1996; Eritsland, et al., 1995; Sacks, et al., 1995; Eritsland, et al., 1994; Leaf, et al., 1994; Sirtori, et al., 1998). Taken together, these studies did not find beneficial effects, i.e., a lowering of LDL cholesterol, from omega-3 fatty acids.

Finally, *Dietary Guidelines for Americans*, 2000 states that studies are underway to determine if there is a relationship between omega-3 fatty acids and CHD disease, indicating, as do the mixed results of the observational studies, that there is uncertainty regarding whether intake of omega-3 fatty acids per se may be related to reduced risk of CHD. Therefore, based on its scientific review, which included evaluation of recent studies submitted to the agency as comments, the agency's own review of the scientific data and information, and the uncertainty expressed in the recent statement in *Dietary Guidelines for Americans*, 2000, FDA concludes that there is not significant scientific agreement among qualified experts that the available evidence supports a relationship between intake of omega-3 fatty acids and reduced risk of CHD in the general population.

In sum, there are no studies that demonstrate a causal relationship between the specific substance (the EPA and DHA omega-3 fatty acids) and reduction of the risk of the specific disease or health-related condition (CHD) in the general population. Therefore, the agency finds that the more recent data do not alter the previous 1993 conclusion that the scientific evidence is not sufficiently definitive for a relationship between omega-3 fatty acids per se and reduced risk of CHD in the general population. Based on its evaluation of the totality of the publicly available scientific evidence, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between omega-3 fatty acids and reduced risk of CHD.

VI. The Agency's Consideration of a Qualified Claim

In the Pearson implementation notice, the agency stated that it would consider exercising enforcement discretion for a dietary supplement health claim when the following conditions are met: (1) The claim is the subject of a health claim petition that meets the requirements of § 101.70; (2) the scientific evidence in support of the claim outweighs the scientific evidence

against the claim, the claim is appropriately qualified, and all statements in the claim are consistent with the weight of the scientific evidence; (3) consumer health and safety are not threatened; and (4) the claim meets the general requirements for health claims in § 101.14, except for the requirement that the evidence supporting the claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. The first prong does not apply to this decision since the agency is complying with an instruction by the court to reconsider the claim, as discussed earlier. Thus, in the absence of significant scientific agreement, and based on its conclusion that the use of EPA and DHA omega-3 fatty acids as dietary supplements is safe and lawful under 21 C.F.R. § 101.14, provided that daily intakes of EPA and DHA omega-3 fatty acids do not exceed 3 g/p/d from conventional food and dietary supplement sources, FDA has considered, under *Pearson*, whether the weight of the scientific evidence in support of the claim outweighs the scientific evidence against the claim and, if so, whether the use of a qualified claim would be safe.

A. Weight of the Scientific Evidence

The intervention trials in a diseased population with omega-3 fatty acids and CHD as the endpoint provide the strongest evidence for a relationship between omega-3 fatty acids and reduced risk of CHD (GISSI Prevensione Investigators, 1999; von Schacky, et al., 1999; Singh, et al., 1997; Burr, et al., 1994). These studies directly measured exposure to the substance that is the subject of the claim, omega-3 fatty acids (i.e., EPA, DHA) (Table 1) and also measured disease endpoints (e.g., cardiovascular death, congestive heart failure, myocardial infarction, or stroke). These intervention trials were randomized controlled clinical trials, which are considered the most persuasive studies, and they all showed a relationship between intake of omega-3 fatty acids and reduced risk of CHD in a diseased population (i.e., subjects with diagnosed CHD or recent myocardial infarctions). However, there are no corresponding studies supporting a direct (causal) relationship between omega-3 fatty acid intake and reduced risk of CHD in a general population. Thus, uncertainty remains regarding whether the relationship of omega-3 fatty acid intake and reduced risk of CHD found in a diseased population would be seen in the general population.

FDA evaluated other available evidence to determine whether there was a sufficient basis to support a qualified claim for omega-3 fatty acids and reduced risk of CHD. FDA evaluated two types of studies: (1) Observational studies in the general population in which fish consumption was the primary contributor of omega-3 fatty acids, and (2) intervention studies in both general and diseased populations that evaluated the effects of omega-3 fatty acids on LDL cholesterol, a surrogate marker for CHD risk.

FDA focused on observational studies in the general population (Ascherio, et al., 1995; Guallar, et al., 1999; Daviglus, et al., 1997; Pietinen, et al., 1997; Albert, et al., 1998; Kromhout, et al., 1996; Rodriguez, et al., 1996; Guallar, et al., 1995; Kromhout, et al., 1995; Morris, et al., 1995; Simon, et al., 1995; Siscovick, et al., 1995; Yamori, et al., 1994). The agency sought to determine whether these studies could provide a plausible basis for presuming that the relationship between omega-3 fatty acids and the reduced risk of CHD in the diseased population supports a suggested relationship in the general population. The

observational studies with CHD endpoints provide less compelling evidence than intervention studies for a relationship between omega-3 fatty acids and reduced risk of CHD because they did not measure omega-3 fatty acid intakes directly, and they cannot separate the effect of omega-3 fatty acids from the effects of other food components. Moreover, they cannot establish causality.

Taken together, as discussed in Section IV.B.2, the observational studies show mixed effects, some beneficial (Daviglus, et al., 1997; Albert, et al., 1998; Kromhout, et al., 1996; Rodriguez, et al., 1996; Kromhout, et al., 1995; Simon, et al., 1995; Siscovick, et al., 1995; Yamori, et al., 1994), some showing no relationship (Ascherio, et al., 1995; Guallar, et al., 1999; Guallar, et al., 1995; Morris, et al., 1995), and one suggesting adverse effects (Pietinen, et al., 1997). The observational studies were mixed. However, as discussed below, because physiological measures, such as triglycerides, VLDL cholesterol, and platelet aggregation, respond similarly to intakes of omega-3 fatty acids in both diseased and general populations, the evidence is suggestive of a relationship between omega-3 fatty acids and reduced risk of CHD in the general population.

FDA also evaluated the usefulness of intervention trials that studied LDL cholesterol as a surrogate marker for CHD, and trials that examined other physiological measures, to determine whether any similar effects, other than reduced CHD risk, were seen in both diseased and general populations in response to omega-3 fatty acid intake. Generalizing from a high risk (diseased) population to the general (healthy) population is difficult because of uncertainty as to whether the diseased population has a unique responsiveness to effects of omega-3 fatty acids that would not be found in the general population.

Omega-3 fatty acids showed similar effects in diseased and general populations relative to several physiological measures. For example, most studies in both diseased and general populations showed no effect of omega-3 fatty acid intakes on LDL cholesterol levels (Sorensen, et al., 1998; Vognild, et al., 1998; Grimsgaard, et al., 1997; Hwang, et al., 1997; Marckmann, et al., 1997; Agren, et al., 1996; Hamazaki, et al., 1996; Layne, et al., 1996; Lervang, et al., 1993; Deslypere, 1992; Schmidt, et al., 1992; GISSI Prevensione Investigators, 1999; Cairns, et al., 1996; Eritsland, et al., 1996; Eritsland, et al., 1995; Sacks, et al., 1995; Eritsland, et al., 1994; Leaf, et al., 1994). Therefore, FDA concluded that the observed beneficial effects of omega-3 fatty acids on CHD risk in diseased populations do not appear to be operating through a mechanism of lowering LDL cholesterol (see section IV.B.1).

Additionally, in both general and diseased populations, omega-3 fatty acids generally reduced triglycerides, (56 Fed. Reg. at 60,669; 58 Fed. Reg. at 2691) and very-low-density lipoprotein (VLDL) cholesterol (56 Fed. Reg. at 60,669; 58 Fed. Reg. at 2691), and had no effect on total serum cholesterol (56 Fed. Reg. at 60,663) or HDL cholesterol (56 Fed. Reg. at 60,663; 58 Fed. Reg. at 2691, 2701). In both diseased and general populations, omega-3 fatty acids generally increased standardized bleeding times (56 Fed. Reg. at 60,670), reduced platelet aggregation (56 Fed. Reg. at 60,671; 58 Fed. Reg. at 2696, 2702), and reduced postprandial lipemia (58 Fed. Reg. at 2692).

Thus, in many studies of intakes of omega-3 fatty acids, similar physiological effects are seen in diseased and general populations. Similar effects are seen on a surrogate marker for CHD and on other physiological effects associated with CHD risk. Because these physiological markers respond similarly to intakes of omega-3 fatty acids in both diseased and general populations, these studies suggest, but do not establish, that omega-3 fatty acids may have similar effects in both groups relative to CHD risk-reduction effects.

Based on its review of the scientific evidence, FDA concludes that the weight of the scientific evidence for a claim relating EPA and DHA omega-3 fatty acids and reduced risk of CHD outweighs the scientific evidence against the claim because: (1) The evidence from intervention trials with CHD as an endpoint is strongly favorable in a diseased population showing that omega-3 fatty acid intake is related to reduced risk of CHD; (2) there is suggestive evidence that the benefit on CHD reported in diseased populations will carry over to the general population because omega-3 fatty acids have similar physiological effects in both diseased and general populations; and (3) in view of the data in diseased populations and the evidence from observational trials in the general population, with CHD as an endpoint, the scientific evidence is suggestive of a relationship between omega-3 fatty acids and reduced risk of CHD.

B. Consumer Health and Safety

FDA concluded in its safety review (section III above), that the use of EPA and DHA omega-3 fatty acids as a dietary supplement is safe and lawful under 21 C.F.R. § 101.14, provided that daily intakes of EPA and DHA omega-3 fatty acids do not exceed 3 g/p/d from conventional food and dietary supplement sources. The agency noted that the safety evaluation for its GRAS affirmation of menhaden oil did not include intakes of EPA and DHA from dietary supplements or from other ingredient and food sources of EPA and DHA in conventional foods other than menhaden oil. The safety concerns for the use of EPA and DHA omega-3 fatty acids in dietary supplements would be the same as those identified for these omega-3 fatty acids in menhaden oil added to conventional foods. Thus, FDA finds that the use of EPA and DHA omega-3 fatty acids as a dietary supplement will be safe and lawful under 21 C.F.R. § 101.14, provided that total intakes of EPA and DHA omega-3 fatty acids are limited to 3 g/p/d from all sources, including conventional food sources and dietary supplement sources.

To ensure the safety of EPA and DHA dietary supplements bearing a qualified health claim for omega-3 fatty acids and reduced risk of CHD, FDA first considered the likely impact of such a claim on exposure to omega-3 fatty acids.

1. Impact on Intakes of EPA and DHA Omega-3 Fatty Acid Dietary Supplements Bearing a Qualified Health Claim for Omega-3 Fatty Acids and Reduced Risk of CHD

At present, the estimated mean exposure to EPA and DHA from menhaden oil in all food categories is 2.8 g per person per day (62 Fed. Reg. at 30,754). This is a conservative estimate with substantial margin for safety, and the agency believes that the addition of menhaden oil to food products has not come close to this conservative mean exposure

estimate. The question, then, is whether intakes of EPA and DHA would be likely to remain within safe limits if a qualified health claim for omega-3 fatty acids and reduced risk of CHD were to appear on dietary supplements.

Exposure estimates for current intakes of EPA and DHA omega-3 fatty acids are difficult to make because FDA does not have data on the amount of menhaden oil currently being added to foods and consumed or on intakes of omega-3 fatty acids from dietary supplements and other food sources. It is likely, however, that intakes of EPA and DHA omega-3 fatty acids have increased since the GRAS affirmation rulemaking for menhaden oil because of the availability of foods with added menhaden oil. Further, increased intakes are likely because of the availability of EPA and DHA in other oils rich in omega-3 fatty acids, the presence of EPA and DHA in poultry fed on fish meal, and eggs containing omega-3 fatty acids (see Kris-Etherton, et al., 2000; Raper, et al., 1992; see also, Memo to File in Docket 91N-0103 – "Sources of Omega-3 Fatty Acids" October 30, 2000).

Similarly, higher intakes from dietary supplement sources are likely. Sales between 1995 and 1999 of dietary supplements of fish oils and omega-3 fatty acids in supermarkets, drug stores, and mass merchandiser outlets have increased from 14.6 to 22.4 million dollars, more than a 50 percent increase in annual dollar sales (see Memo to File in Docket 91N-0103 – "IRI Market Data" October 20, 2000). Furthermore, these figures do not include sales at health food stores or through the Internet.

FDA has received more than 70 notifications under 21 C.F.R. § 101.93 for structure/function claims for omega-3 fatty acids and fish oils, which contain omega-3 fatty acids. These claims provide consumers with exposure to a variety of claimed benefits for omega-3 fatty acids and fish oils (See Memo to File in Docket 91N-0103 - "Structure/Function Claims for Omega-3 Fatty Acids and Fish Oils - Notifications under 21 CFR 101.93" October 30, 2000). Furthermore, FDA-approved health claims have been shown to increase sales and encourage intake of related products (See Memo to ONPLDS from DMS in Docket 91N-0103 – "Health Claims and Product Sales" October 27, 2000). Thus, a qualified health claim on a dietary supplement containing EPA and DHA omega-3 fatty acids would be likely to increase sales of and dietary exposure to EPA and DHA omega-3 fatty acids.

It is likely that a qualified claim for EPA and DHA omega-3 fatty acids would increase sales and consumption of omega-3 fatty acids. Moreover, given that dietary supplements are concentrated sources of omega-3 fatty acids, intakes from dietary supplements can easily overwhelm food uses. For example, FDA has found that recommended daily intakes on omega-3 fatty acid products, based on information provided on product labels, are commonly around 300 to 1,000 mg per day but may be as high as 3,000 to 5,000 mg per day (with a few isolated products even higher)(see Memo to File in Docket 91N-0103 – "Survey of currently marketed products containing Omega-3 fatty acids with DHA and EPA" October 24, 2000). By contrast, although a 4-ounce (112 gram) portion of salmon may contain 900 mg of omega-3 fatty acids (calculated from data provided in Raper, et al., 1992), daily consumption of salmon is unlikely in the general population. Thus, a consumer taking a more concentrated source of EPA and DHA omega-3 fatty acids as a dietary supplement, could easily exceed the likely amount of such fatty acids present in fish.

FDA is concerned that if a qualified health claim for EPA and DHA omega-3 fatty acids and reduced risk of CHD were to appear on dietary supplement products, intakes of such omega-3 fatty acids might increase to levels in excess of the safe upper level, i.e., in excess of 3 g/p/d. As previously discussed, more products containing omega-3 fatty acids are now available, there are omega-3 fatty acid dietary supplements that bear structure/function claims, and dietary supplements provide the opportunity to consume large amounts of omega-3 fatty acids. To help ensure that consumers do not exceed a 3 g/p/d intake from conventional food and EPA and DHA omega-3 fatty acid dietary supplements that bear the qualified claim, FDA intends to exercise its enforcement discretion with respect to the use of the qualified claim on omega-3 fatty acid dietary supplements that do not recommend or suggest in their labeling, or under ordinary conditions of use, daily intakes of more than 2 grams EPA and DHA.

2. FDA's Exercise of Enforcement Discretion With Respect to the Use of a Qualified Health Claim for Omega-3 Fatty Acids and Reduced Risk of CHD on Dietary Supplements

FDA considered two approaches to address safety concerns associated with high intakes of omega-3 fatty acids: (1) Label statements, and (2) limits on amounts of EPA and DHA contained in dietary supplements. There are several reasons why label statements alone, e.g., "Don't consume more than 3 grams of EPA and DHA omega-3 fatty acids from all sources," would not be sufficient to help ensure that consumers do not consume more than 3 grams of omega-3 fatty acids daily, levels for which FDA has no assurance of safety. Not all at-risk consumers can determine if they are at risk. In the final rule for the professional labeling of aspirin, FDA noted that with regard to the use of aspirin to prevent vascular events (e.g., stroke, MI, or cardiovascular death) and other thromboembolic conditions, consumers are not able to determine if they are at risk of adverse events associated with prolonged use. Such adverse events include bleeding tendencies and their associated risk of hemorrhagic stroke and other serious consequences (63 Fed. Reg. 56,802 at 56,809). The agency concluded that it is not possible to provide adequate directions and warnings to enable the layperson to make a reasonable self-assessment of these factors (*id.* at 56,809). Similarly, consumers do not have the ability to make a reasonable self-assessment of their risks associated with long-term use of high intakes of omega-3 fatty acids.

Consumers trying to stay within a 3 g/p/d limit of omega-3 fatty acids would not be able to accurately estimate their current intake. Fatty fish, the most common source of omega-3 fatty acids in the diet, vary in the amount of omega-3 fatty acids that they may contribute (Kris-Etherton, et al., 2000). Further, there are other dietary sources of omega-3 fatty acids in the food supply from which a consumer would not necessarily be able to calculate the contribution of omega-3 fatty acids. Examples of such foods include those with added menhaden oil, other oils rich in omega-3 fatty acids, the presence of EPA and DHA in poultry fed on fish meal, and in eggs containing omega-3 fatty acids (Kris-Etherton, et al., 2000; Raper, et al., 1992) (see Memo to File in Docket 91N-0103 – "Sources of Omega-3 Fatty Acids" October 30, 2000).

Furthermore, information on omega-3 fatty acid content is not generally available on the labeling of foods and not uniformly available on dietary supplements. No Reference Daily

Intake (RDI) or Daily Reference Value (DRV) has been established for omega-3 fatty acids; therefore, the omega-3 fatty acid content is prohibited from appearing on labels of conventional foods in the Nutrition Facts Panel (21 C.F.R. § 101.9(c)). The omega-3 fatty acid content would be listed outside of the Nutrition Facts Panel if a manufacturer made a percent or an amount claim for omega-3 fatty acids under 21 C.F.R. § 101.13(i)(3), but manufacturers are not required to make such claims on their products containing omega-3 fatty acids. For example, although fish are the most common food source of omega-3 fatty acids (Raper, et al., 1992; Kris-Etherton, et al., 2000), there is no requirement to list the omega-3 fatty acid content on the label of fish products; therefore, people who consume fish and fish products would not necessarily be able to tell how much omega-3 fatty acids they are consuming.

The labeling of dietary supplement products containing omega-3 fatty acids are regulated under 21 C.F.R. § 101.36(b)(3), which describes the information required for dietary ingredients for which neither an RDI nor a DRV has been established. Dietary ingredients of this type are required to be listed by their common or usual name with a footnote indicating that a Daily Value has not been established (See example in the September 23, 1997, final rule on the labeling of dietary supplements; 62 Fed. Reg. 49,826 at 49,855). Therefore, omega-3 fatty acid content would be included on dietary supplement products that specify that they contain omega-3 fatty acids. However, manufacturers of fish oil capsules could list the specific fish oil as the dietary ingredient (e.g., Cod Liver Oil) and would not be required to include the omega-3 fatty acid content on the label. Thus, although fish oils contain significant amounts of EPA and DHA, this information would not necessarily be available to consumers on dietary supplement product labels of fish oils containing omega-3 fatty acids.

In short, information on omega-3 fatty acid content is not uniformly available on the labeling of conventional food or dietary supplement products that contain omega-3 fatty acids. Therefore, it is not possible for consumers to accurately estimate their intakes of omega-3 fatty acids from food or dietary supplement sources to ensure that their intakes do not exceed 3 g/p/d.

Consumers could not estimate their intake of omega-3 fatty acids from all conventional food or dietary supplement product labeling. Accordingly, FDA has determined that a label statement on a dietary supplement bearing the qualified health claim for omega-3 fatty acids and reduced risk of CHD could not itself ensure that daily intake by a consumer who consumes the supplement is not greater than 3 g/p/d of omega-3 fatty acids. Therefore, FDA has determined that it is necessary to provide a limit on the amount of EPA and DHA that may be recommended or suggested in the labeling, or under ordinary conditions of use[5], of a dietary supplement bearing the qualified claim. Thus, for such a dietary supplement to be within the scope of FDA's enforcement discretion outlined in this letter, the supplement would need to limit the amount suggested or recommended in the labeling or under ordinary

[5] For a dietary supplement to not be considered adulterated under section 402(f) of the act, it must not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use. Further, a dietary supplement must not contain a dietary ingredient that may render it injurious to health under the conditions of use recommended or suggested in the labeling of such dietary supplement.

conditions of use to a daily intake of no more than 2 grams of EPA and DHA from such supplement. The agency believes that such a 2-gram per day limit is reasonable, based on estimates of current dietary intakes of foods that naturally contain EPA and DHA and of other sources of EPA and DHA in food products.

Raper and Kris-Etherton used food disappearance data to estimate per capita intakes of EPA and DHA of 124 mg/day (0.1 g/day) in 1985 (Raper, et al., 1992) and between 100 and 200 mg/day (0.1-0.2 g/day) from 1989-1991 (Kris-Etherton, et al., 2000), respectively. However, food disappearance data are notoriously difficult to use as estimates of intake, especially of fats and oils (Kris-Etherton, et al., 2000). Per capita estimates divide total amounts of foods available for consumption by the total population. They do not take into account that some people consume a lot of foods rich in omega-3 fatty acids and others consume very little.

In estimating possible intakes, FDA considered recent intake estimates and data from several sources. The American Heart Association (AHA) (Krauss, et al., 2000) recently noted that one fatty fish meal per day could result in an omega-3 fatty acid intake (i.e., EPA and DHA) of 900 mg (0.9 g) per day. A four-ounce (112 g) serving of Coho salmon provides 900 mg (0.9 g) EPA and DHA; a similar four-ounce (112 g) serving of Atlantic mackerel provides 2,600 mg (2.6 g) EPA and DHA (values calculated from omega-3 fatty acid content data in Raper, et al., 1992).

There is additional variability in the estimates of omega-3 fatty acid intakes because there are limited data on population sub-groups who are frequent consumers of fish. Although Rodriquez, et al. (1996), indicated that more than 50 percent of the Japanese-American men in their study reported consuming fish fewer than two times per week, 40 percent reported eating fish two to four times per week, and 7 percent reported eating fish nearly every day. Morris, et al. (1995), reported that 5 percent of the men in the Physicians' Health Study consumed fish five or more times a week, and on average, the men consumed 2.1 meals containing fish per week. Thus, there are consumers who eat fish every day, or nearly every day, and average intakes of omega-3 fatty acids from fish consumption alone in those consumers could be nearly 1 gram per day from a fatty fish meal (Krauss, et al., 2000). Frequent consumers of Atlantic mackerel could be consuming amounts of omega-3 fatty acids approaching 3 g/d. However, most fish contain significantly lower levels of omega-3 fatty acids than Atlantic mackerel (Raper, et al., 1992; Kris-Etherton, et al., 2000). Therefore, even frequent consumers of fish are likely to be consuming well below 3/p/d of omega-3 fatty acids from fish. Those people who do not consume fish on a daily basis would also likely consume well below 3 g/p/d omega-3 fatty acids.

There is uncertainty as to baseline levels of intake of omega-3 fatty acids in the general population and in population subgroups who are consumers of omega-3-fatty acid-rich foods. Nonetheless, based on the information available to the agency on potential intakes from omega-3 fatty acid food sources, FDA believes that a consumer could consume nearly 1 gram per day in the diet from conventional foods. As stated previously, average intakes of consumers who include a fatty fish meal every day, or nearly every day, could be consuming about 1 gram per day.

The epidemiologic data on fish consumption suggest that intakes of omega-3 fatty acids below 1 gram per day might have some possibility of having a beneficial effect on reducing CHD risk. Dietary supplement products with recommended intakes of 1 gram or below per day would provide an added safety margin for consumers to remain below the 3-gram safety limit. Given the uncertainties in current intakes, the potential for harm from excessive intakes, and the possibility of benefit at intakes less than 1 gram per day, FDA encourages manufacturers to limit their dietary supplement products bearing the qualified health claim to products recommending or suggesting daily intakes of 1 gram or less of EPA and DHA omega-3 fatty acids.

3. Conclusion

FDA concludes that the use of EPA and DHA omega-3 fatty acids as dietary supplements is safe and lawful under 21 C.F.R. § 101.14, provided that daily intakes of EPA and DHA omega-3 fatty acids do not exceed 3 g/p/d from conventional food and dietary supplement sources. Further, FDA concludes that in order to help ensure that a consumer does not exceed an intake of 3 g/p/d of EPA and DHA omega-3 fatty acids from consumption of a dietary supplement with the qualified claim, an EPA and DHA omega-3 fatty acid dietary supplement bearing a qualified claim should not recommend or suggest in its labeling, or under ordinary conditions of use, a daily intake exceeding 2 grams EPA and DHA.

FDA is basing its decision, in part, on the information available to the agency on increased sales that result when products bear health claims, on current uses of menhaden oil allowed in foods, and on consumption of other foods that contain significant amounts of omega-3 fatty acids. However, there is considerable uncertainty as to actual intakes of omega-3 fatty acids. Therefore, FDA will be monitoring the marketplace and making the best estimates possible to ensure that EPA and DHA omega-3 fatty acid supplements bearing the qualified claim remain safe.

FDA would consider supplements that encourage intakes (in the labeling or under ordinary conditions of use) above 2 grams per day to be misbranded under section 403(a) of the Federal Food, Drug, and Cosmetic Act (the act). Such labeling would be misleading under section 201(n) of the act with respect to consequences which may result from the use of the supplement. Consequences include a potential risk of excessive bleeding in some individuals with intakes of EPA and DHA omega-3 fatty acids at levels in excess of 3 grams (62 Fed. Reg. at 30,753). As previously stated, the agency is encouraging manufacturers to limit the products that bear the qualified claim for omega-3 fatty acids and reduced risk of CHD to a daily intake of 1 gram or below. Further, dietary supplements that bear the qualified claim that encourage intakes (in labeling or under ordinary conditions of use) above 2 grams per day would be subject to regulatory action as a misbranded food under section 403(r)(1)(B) of the act (21 U.S.C. 343(r)(1)(B)), a misbranded drug under section 502(f)(1) of the act (21 U.S.C. 352(f)(1), as an unapproved new drug under section 505(a) of the act (21 U.S.C. 355(a)).

C. Qualified Claim Language

In its decision, the *Pearson* court suggested a disclaimer along the following lines: "The evidence is inconclusive because existing studies have been performed with *foods* containing [omega-3 fatty acids], and the effect of those foods on reducing the risk of [coronary heart disease] may result from other components in those foods." 164 F.3d at 658 (emphasis in the original).

FDA finds that this qualified claim is not entirely consistent with the weight of the evidence. The language suggested by the court merely states that the evidence is inconclusive, which could mean that the weight of the scientific evidence in support of the claim is equivalent to the weight of the scientific evidence against the claim. Having evaluated evidence for the relationship between omega-3 fatty acids and reduced risk of CHD, the agency concludes that the evidence is suggestive, not just merely inconclusive.

The agency would consider the following claim to be appropriately qualified: "The scientific evidence about whether omega-3 fatty acids may reduce the risk of coronary heart disease (CHD) is suggestive, but not conclusive. Studies in the general population have looked at diets containing fish and it is not known whether diets or omega-3 fatty acids in fish may have a possible effect on a reduced risk of CHD. It is not known what effect omega-3 fatty acids may or may not have on risk of CHD in the general population."

The relevant elements in this claim include: (1) The scientific evidence is suggestive but not conclusive for a relationship between omega-3 fatty acids and reduced risk of CHD in the general population; (2) the studies in the general population have looked at diets containing fish and not at omega-3 fatty acids and have not shown whether diets or omega-3 fatty acids in fish may have a possible effect on a reduced risk of CHD; and (3) it is not known what effect omega-3 fatty acids may or may not have on risk of CHD in the general population. A dietary supplement bearing a claim that is not properly qualified or consistent with the weight of the evidence is subject to regulatory action as a misbranded food under section 403(r)(1)(B)), a misbranded drug under section 502(f)(1)), and as an unapproved new drug under section 505(a)).

D. Relevant 21 CFR 101.14 Requirements

Consistent with the Pearson implementation notice, the agency intends to exercise its enforcement discretion with respect to the qualified claim when the claim meets the general requirements for health claims in 21 C.F.R. § 101.14 (65 Fed. Reg. at 59,856). FDA finds that the provision in Section 101.14(d)(2)(vii) stating, "If the claim is about the effects of consuming the substance at other than decreased dietary levels, . . . the claim must specify the daily dietary intake necessary to achieve a claimed effect . . .." does not apply to the qualified claim for EPA and DHA omega-3 fatty acids and reduced risk of CHD. The scientific evidence for this relationship is merely suggestive and does not support the establishment of a recommended daily dietary intake level or even a possible level of effect. Therefore, the agency would consider any labeling suggesting a level of omega-3 fatty acids to be useful in achieving a claimed effect to be false and misleading under section 403(a) of the act.

Moreover, compliance with certain criteria in § 101.14 will have to be evaluated after-the-fact, because they involve information or circumstances that cannot be determined *a priori*. For example, FDA will not be able to determine whether the entire claim appears in one place without intervening material, as required by § 101.14(d)(2)(iv), until it actually sees the claim on products in the marketplace.

E. Other Considerations

EPA and DHA omega-3 fatty acid dietary supplements bearing the qualified claim, which meet the conditions for the exercise of FDA's enforcement discretion in the Pearson implementation notice and the other conditions set forth in this letter, must still meet all applicable statutory and regulatory requirements under the act. For example, such supplements must be labeled consistent with 21 C.F.R. § 101.36(b)(3). Such supplements should be manufactured in a manner that will not adulterate or misbrand the product. Dietary supplements must not pose an unreasonable risk of illness or injury to the consumer or contain substances that may render the product injurious to health.

VII. Conclusion

FDA has set forth conditions, consistent with, and in addition to, those described in the Pearson implementation notice, under which it intends to exercise enforcement discretion with respect to the use of the qualified claim, as described above, on EPA and DHA omega-3 fatty acid dietary supplements.

The conditions in question include that EPA and DHA omega-3 fatty acids in supplements bearing the qualified health claim not recommend or suggest in the labeling, or under ordinary conditions of use, intakes of more than 2 grams per day. As previously stated, FDA encourages manufacturers to limit their dietary supplement products, bearing the qualified health claim, to products recommending or suggesting in the labeling daily intakes of 1 gram or less of EPA and DHA omega-3 fatty acids per day. This would provide an added safety margin for consumers to remain below the 3 gram per day level.

FDA also concludes that there is not significant scientific agreement for an unqualified claim about the relationship between EPA and DHA omega-3 fatty acids and reduced risk of CHD. Thus, a health claim stating that "Omega-3 fatty acids may reduce the risk of CHD" would be misleading. However, the weight of the scientific evidence for a health claim for EPA and DHA omega-3 fatty acids outweighs the scientific evidence against such a claim, and the qualified claim that FDA has set forth in this letter is consistent with the weight of the scientific evidence.

Scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new evidence that becomes available to determine whether the weight of the evidence shifts, either in favor of an unqualified claim or in favor of no longer exercising enforcement discretion. For example, scientific evidence may later become available that will support significant scientific agreement or that will no longer support the use of a qualified claim, or that may raise safety concerns about the conditions that FDA has outlined for the

safe use of this qualified claim. If and when such information becomes available, FDA intends to inform you of that by letter.

We hope that this clarifies the issues related to the labeling of your product.

Sincerely yours

Christine J. Lewis, Ph.D.
Director
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Enclosures: References
Tables 1, 2, and 3

Omega-3 Fatty Acids and Coronary Heart Disease
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Attachment: Health Claim - Omega-3 Fatty Acids and Coronary Heart Disease (Docket No. 91N-0103)

Table 1. **Omega-3 Fatty Acids and Coronary Heart Disease Intervention Studies Disease Outcome**

Reference	Intake* [EPA+DHA or or FO or *n*-3 FA- g/d]	Study Duration+	Population∀ [no. & characteristics]	Disease Outcome♦
GISSI, et al., 1999	0.850-0.882 g/d EPA+ DHA (Ethyl esters)	3.5 yr.	11,324, MI	↓ CVD death, non-fatal MI
Von Schacky, et al., 1999	6 g/d *n*-3 (FO) 3 g/d *n*-3 (FO)	3 mo. 21 mo.	223, PTCS	↓ CVD death, fatal & non-fatal MI
Singh, et al., 1997	1.8 g/d EPA+ DHA (FO)	1 yr.	360, MI	↓ Cardiac deaths, non-fatal MI
Burr, et al., 1994	3 g/d FO	2 yr.	227, MI	↓ CHD deaths

Footnote : Abbreviations and notations Table 1

*Symbols for intake in g/d include: FO - Fish Oil; *n*-3 - omega-3 fatty acids; FA – fatty acid; DHA - doscosahexaenoic acid; EPA- eicosapentaenoic acid; DHA + DPA (FO) - amount of DHA and EPA from fish oil; g – grams; d – day.

+Symbols for study durations include: yr. – year, mo. – month; d – day.

∀Symbols for description of population at time of enrollment: MI - Myocardial Infarction; PTCS - Percutaneous Transluminal Coronary Stenosis; PTCA Percutaneous Transluminal Coronary Angioplasty; CVD - Cardiovascular Disease; CHD - Coronary Heart Disease. Representative of CHD disease patients.

♦ Symbol for intervention effect measures: NS – non-significant; ↑ - increase in risk of CHD or CVD; ↓ - decrease in risk of CHD or CVD.

Attachment: Health Claim - Omega-3 Fatty Acids and Coronary Heart Disease (Docket No. 91N-0103)

Table 2.

Omega-3 Fatty Acids and Coronary Heart Disease
Intervention Studies
Low Density Lipoprotein Cholesterol (LDL-C)

Reference	Intake* [EPA+DHA or or FO or *n*-3 FA g/d	Study Duration+	Population∀ [no & characteristics]	LDL-C ♦
Sorensen, et al., 1998	0.91 g/d EPA+DHA (FO)	1 mo.	47, General∞	NS
Vognild, et al., 1998	15 ml/d WO, SO or CLO	3 mo.	266, General	NS
Alder, et al., 1997	3.6 g/d EPA+DHA (FO)	4 mo.	50, General	↑
Grimsgaard, et al., 1997	3.8 g/d EPA or 3.6 g/d DHA Ethyl esters	7 wk.	234, General	NS
Hwang, et al., 1997	6 to 15 g/d *n*-3 g/d (FO)	2.8 mo.	68, General	NS
Marckmann, et al., 1997	0.91 g/d *n*-3 FA (FO-margarine)	3.5 mo.	50, General	NS
Morcos, 1997	3.0 g/d EPA+DHA (FO)	2 mo.	40, General	↓
Tsai, et al., 1997	8.8 g/d EPA + DHA (FO)	6 wk.	16, General	NS
Agren, et al., 1996	2.28 g/d EPA+DHA (FO) 1.68 DHA oil 1.05 g/d EPA + DHA (fish diet)	3.6 mo.	55, General	NS NS NS
Hamazaki, et al., 1996	1.5 - 1.8 g/d DHA	3 mo.	35, General	NS
Layne, et al., 1996	35 mg/kg body wt (FO)	9 mo.	26, General	NS
Mori,et al., 1993	2.12 g/d EPA+DHA (FO)	3 mo.	120, mild HC	↑
Hansen, et al., 1993	5.3 g/d EPA+DHA (CLO)	7 mo.	34, General	males↑; females NS

Lervang,et al., 1993	0.64 g/d (FO)	2 mo.	24, General	NS
Deslypere, et al., 1992	1.12, 2.24, or 3.37 g/d (FO)	18 mo.	58, General	NS
Schmidt, et al., 1992	3.2 g/d EPA+DHA (FO)	1 yr.	24, General	NS
GISSI, et al., 1999	0.85-0.88 g/d EPA+DHA (Ethyl esters)	3.5 yr.	9659, MI	NS
Cairns, et al., 1996	5.4 g/d *n*-3 FA (FO)	5 mo.	814, PTCA	NS
Eritsland, et al., 1996	4.22 g/d EPA+DHA (FO)	1 yr.	617, CAB	NS
Eritsland, et al., 1995	3.4 g/d EPA + DHA (FO)	1 yr.	511, CABG	NS
Sacks, et al., 1995	6 g/d EPA+DHA+DPA (F0)	2.3 yr.	59. CHD	NS
Eritsland, et al., 1994	3.4 g/d EPA + DHA (FO)	6 mo.	57, CABG	NS
Leaf, et al., 1994	6.9 g/d EPA+DHA (FO)	6 mo.	447, PTCA	NS
Sirtori, et al., 1998	1.72 - 2.58 g/d EPA+DHA (FO)	1 yr.	868, Type IIB and Type IV	↑

Footnote: Abbreviations and notations Table 2

[*] **Symbols for intake in g/d include**: FO - Fish Oil; *n*-3 - omega-3 fatty acids; FA – fatty acid; DHA - doscosahexaenoic acid; EPA- eicosapentaenoic acid; DHA + EPA (FO) - amount of DHA and EPA from fish oil; g – grams; kg – kilogram; wt – weight; d – day; ml - milliliter; WO – whale oil; SO - Seal oil; CLO - Cod liver oil.

[+] **Symbols for study duration include**: yr. – year, mo. – month; wk – week; d – day.

[∀] **Symbols for description of population at time of enrollment**: MI - Myocardial Infarction; PTCS - Percutaneous Transluminal Coronary Stenosis; PTCA Percutaneous Transluminal Coronary Angioplasty; HC – hyper-cholesterolemia; CAB – Coronary Artery Bypass; CABG - Coronary Artery Bypass Grafting; CHD - Coronary Heart Disease; Type IIB and Type IV – types of hyperlipiproteinemia. Representative of CHD disease patients and general population.

[∞] General population is defined as free of indications of CHD.

[♦] **Symbol for intervention effect measures**: NS – non-significant; ↑ - increase in LDL; ↓ -decrease in LDL; LDL – Low density lipoprotein.

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Table 3. **Omega-3 Fatty Acids and Coronary Heart Disease**
Observational Studies
Disease Outcome

Reference	Type of Study	Intake[•] [EPA+DHA or FO or *n*-3 FA or Fish – g/d] (Source of estimated intake)	Study Duration[+]	Population[∀] [no & characteristics]	Disease Outcome [♦]
Ascherio, et al., 1995 Health Professionals' Follow-up Study	Prospective cohort	Fish (0.07→0.58g/d, *n*-3 FA) 0 to 5 serving/wk , FFQ	10 yr.	44895, General[∞]	NS CHD
Guallar, et al., 1999 EURAMIC Study	Case control	(*n*-3 adipose tissue)		1449, General	NS MI vs DHA
Daviglus, et al., 1997 Western Electric	Prospective cohort	Fish 0 →≥ 35 g/d , FFQ [0; 1-17; 18-34; ≥35g/d]	30 yr.	1822, General	↓ non-sudden death from MI
Pietnen, et al., 1997 ATBC Study	Prospective cohort	Fish (0.2→ 0.8g/d, *n*-3 FA) FFQ	6 yr.	21930, Smokers	↑ *n*-3 fatty acid/fish CHD[X]
Albert, et al., 1998 Physicians' Heath Study	Prospective cohort	Fish (0→ 4x/wk) FFQ	12 yr.	20551, General	↓ sudden cardiac death[Φ]
Kromhout, et al.,1996 Seven Countries Study	Prospective Longitudinal Health survey	Fish (FFQ)	25 yr.	12783, General	↓ CHD mortality
Rodriguez, et al.,1996 Honolulu Heart	Prospective cohort	Fish (0→ >1x/d) (FFQ)	23 yr.	8006, General	↓ CHD mortality[Φ]
Guallar, et al., 1995 Physicians' Health Study	Nested, Case-control	(Blood samples EPA+DHA)	5 yr.	14916, General	NS first MI
Kromhout, et al., 1995	Prospective cohort	Fish (+/-) (diet record)	17 yr.	272, General	↓ CHD death

Morris, et al., 1995 Physicians' Health Study	Prospective cohort	Fish (1→ >5x/wk)	4 yr.	21185, General	NS CVD, MI
Simon, et al., 1995 MRFIT	Nested Case-control	(Blood, DHA & EPA)	3.5 yr.	188, General	↓ CHD risk
Siscovick, et al., 1995 Seattle, WA	Case-control	(Blood), (FFQ) (5.5 g/mo., *n*-3 FA)		827, General	↓ first MI
Yamori, et al., 1994 CARDIAC Study	Population	(Blood), *n*-3 FA & urine, taurine[⊥]		200, General	↓ ischemic heart disease

Footnote: Abbreviations and notations Table 3

[*]**Symbols for intake in g/d include**: FO - Fish Oil; *n*-3 - omega-3 fatty acids; FA – fatty acid; DHA - doscosahexaenoic acid; EPA- eicosapentaenoic acid; DHA + EPA (FO) - amount of DHA and EPA from fish oil; g – grams; d – day; FFQ – Food frequency questionnaire.

[+]**Symbols for study duration include**: yr. – year, mo. – month.

[∀]**Symbols for description of population at time of enrollment**: MI - Myocardial Infarction; CHD - Coronary Heart Disease; CVD - Cardiovascular Disease.

[♦] **Symbol for intervention effect measures**: NS – non-significant; ↑ - increase in risk of CHD or CVD; ↓ -decrease in risk of CHD or CVD.

[∞] General is defined as free of indications of CHD.

[X] Increase in risk CHD using multivariate analysis and highest level of intake of omega-3 fatty acids derived from fish.

[Φ] Decrease in risk of sudden cardiac death and/or CHD mortality associated with highest level of fish intake.

[⊥] Taurine – metabolic product (cysteine), marker for fish protein.